ATTORNEY DOCKET NO. 4830.P RE
PATENT

Reply Under 37 CFR §1.116
Expedited Procedure
Examining Group 1625

#17

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: ROMERO

Serial No. 09/318,534

Filed: May 13, 1999

Title: HETEROCYCLIC AMINES HAVING CENTRAL NERVOUS SYSTEM ACTIVITY

Group Art Unit: 1625

Examiner: P. Morris

Attorney Docket No. 4830.P RE

I hereby certify that this paper is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231.

April 5, 2002

Mark H. Hopkins, Ph.D.
Reg. No. 44,775
Agent for Applicants

PETITION FOR RECONSIDERATION OF RESTRICTION REQUIREMENT UNDER 37 C.F.R. §§ 1.13 AND 1.81

WITH REQUEST FOR EXPEDITED HANDLING

BOX AF
Commissioner For Patents

Washington, DC 20231

Sir:

This petition is submitted under 37 C.F.R. §§ 1.13 and 1.81 to request reconsideration of the restriction requirement in an official action dated January 25, 2001 and the examiner's denial, in a subsequent official action dated October 5, 2001, of the petitioners proper request for reconsideration under 37

C.F.R. § 1.111 dated July 23, 2001. This petition is timely filed concurrently with a Notice of Appeal, and the fee of $130.00 due under 37 C.F.R. § 1.17(h) is authorized to be charged to Marshall, Gerstein, & Borun deposit account number 13-2855. The petitioners respectfully petition for reconsideration in view of the following remarks.

STATEMENT OF THE FACTS INVOLVED

I. THE REQUIREMENT FOR RESTRICTION

In the official action dated January 25, 2001, restriction was required between the claims of Group I (claims 1-12 [sic:8] directed to compounds, composition and use, classified in class 514, subclass 292), Group II (claim 9 directed to an intermediate, classified in class 546, subclass 158), Group III (claim 10 directed to an intermediate, classified in class 546, subclass 159), Group IV (claim 11 directed to an intermediate, classified in class 546, subclass 162), and Group V (claim 12 directed to an intermediate, classified in class 546, subclass 84). At page 3 of the January 25, 2001 Office Action, the Examiner stated that Group I includes claims 1-12. However, applicant believes the Examiner intended Group I to include only claims 1-8, since claims 9-12 are included in Groups II-V, and have been withdrawn from consideration. This appeared to be clarified in the subsequent official action dated October 5, 2001. The restriction requirement is attached as Exhibit 1. The claims are attached as Exhibit 2.

On page 4 of the January 25, 2001 Office Action, Paper No. 12, the examiner, relying upon MPEP §806.04(b), stated that the inventions are patentably distinct because:

> Inventions I and II-V are related as mutually exclusive species in an intermediate-final product relationship. Distinctness is proven for claims in this relationship if the intermediate product is useful to make other than the final product (MPEP §806.04(b), 3rd paragraph), and the species are patentably distinct (MPEP §806.04(h)). In the instant case, the intermediate product is deemed to be useful as herbicides, fungicides, bactericides, insecticides, etc. and the inventions are deemed patentably distinct since there is nothing on this record to show them to be obvious variants.

II. THE PETITIONERS' RESPONSE

The petitioners' proper response and request for reconsideration under 37 C.F.R. § 111 requested withdrawal of the restriction requirement because the search and examination of the entire application could be made without serious burden on the examiner. To satisfy 37 C.F.R. 1.143, the applicants provisionally elected for examination on the merits, with traverse, the claims of Group I, i.e., claims 1-8.

III. THE EXAMINER'S RESPONSE.

In the subsequent official action dated October 5, 2001, the examiner noted the applicants traversal but did not respond to the petitioners arguments and upheld the restriction requirement, maintaining the position that the other inventions represented by claims 9, 10, 11 and 12 will support a separate patent.

POINTS TO BE REVIEWED

The petitioners hereby request review and withdrawal of the requirement for restriction, particularly on the bases that: (1) restriction is not proper because the use that the Examiner suggests is not supported by the record, and therefore the criteria for distinctiveness has not been met; and (2) restriction is not proper because search and examination of the entire application can be made without serious burden on the examiner.

A. Restriction is not proper because the inventions of Groups I-V have not been shown to have separate utility, and the criteria for distinctiveness has not been met

The claims of Group I and Group II-V are related as mutually exclusive species in a final product-intermediate relationship, respectively. Inventions in this relationship are only distinct if it can be shown that the intermediate is useful to make other than the final product (M.P.E.P. § 806.04(b)).

Section 806.04(b) of the M.P.E.P. that the Examiner relies upon also states : "The examiner must give an example of an alternative use but need not provide documentation. Applicant then has the burden to prove or provide a convincing argument that the intermediate does not have the suggested use." The Examiner has alleged that the claims of Groups II-V are useful as "herbicides, fungicides, bactericides, insecticides, etc." although no evidence or scientific reasoning for this contention was provided.

The Applicants contend that the claims of Groups II-V are not known to be useful as herbicides,

fungicides, bactericides, insecticides, etc.. An assertion of such broad utility is ridiculous as compounds that have insecticidal activity generally have very different physical properties from compounds that have herbicidal utility, and so on. Applicants have performed a CAS search of the compounds of claims 9-12 which is attached as Exhibit 3. The search found 2 references to the claimed compounds: The patent of the present reissue proceedings and a subsequent patent, U.S. Patent No. 6,197,339, commonly assigned to Pharmacia & Upjohn directed to formulations to treat Parkinsons disease. No other art was found. There is no evidence in the chemical literature that the claimed compounds have the use that the Examiners suggests.

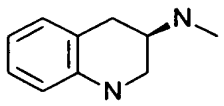
Thus, the standard for restricting Groups I from Groups II-V is not proper on the grounds that the criteria of distinctiveness in M.P.E.P. § 806.04(b) have not been met. This examiner ignores the required criteria of distinctiveness in M.P.E.P. § 806.04(b), that inventions are distinct only "if it can be shown that the intermediate is useful to make other than the final product."

B. Restriction is Not Proper Because Search and Examination of the Entire Application Can Be Made Without Serious Burden on the Examiner

In addition to a showing of distinctiveness, the M.P.E.P. *requires* there to be "reasons for insisting on restriction"...*i.e.*, separate classification, status, or field of search. (See M.P.E.P., §806.05(c), citing §808.02). Likewise, the M.P.E.P. requires that search and examination of the entire application would be a *serious burden* on the examiner. If the search and examination of an entire application can be made without

serious burden, the Examiner must examine it on the merits, even though it arguably may include claims to distinct or independent inventions. MPEP § 803. Restriction is not proper in the present case because search and examination of the entire application can be made without *serious burden* on the examiner.

It is respectfully submitted that the compounds recited in claims 1-12 all possess the following amine-substituted bicyclic core structure:



Thus, the compounds recited in claims 1-12 can be searched and examined without serious burden on the Examiner.

Furthermore, groups II-V are each single claims directed to specific compounds. Searches for these compounds are simple and straightforward. All of the compounds in the claims of Groups II-V were searched on CAS on the Web in 11 minutes and 9 seconds as shown in Exhibit 4. There should be no serious burden on the Examiner in performing the Patent Office's prior art search. Accordingly, it is submitted that the claimed compounds are so closely related that all claims can be included *in one search* without an undue burden on the examiner and should be examined at this time.

Additionally, the Patent and Trademark Office has, on numerous occasions, searched and examined compounds and intermediates, as well as bicyclic and tricyclic compounds together. For example, applicant draws the Examiner's attention to claims 1 and 38 of U.S. Patent No. 5,932,553 (Exhibit 4). This patent discloses tricyclic compounds of claim 1 that are useful as

intermediates for preparing the bicyclic compounds recited in claim 38. See for example, column 14, lines 20-42, where the tricyclic compound HMAF is converted to the bicyclic compound 45. In the '553 application, claims to tricyclic compounds and bicyclic compounds were searched, examined, and allowed in one application. Thus, the action requested by Applicant is not without precedent.

If the Examiner maintains the restriction requirement, applicant requests that Group I (claims 1-8) and Group V (claim 12) should be examined together. The compounds recited by these claims possess a common tricyclic core ring system. It is submitted that the compounds recited in Group I and Group V are likewise sufficiently related such that all recited compounds could be searched simultaneously without an undue burden on the examiner. MPEP § 803. Therefore, if the Examiner maintains the restriction requirement, applicant requests that Group I (claims 1-6) and Group V (claim 12) be examined together.

Finally, claims 9-12 are each directed to a single compound. Because search and examination of all of the claims can be made without *serious burden* (emphasis added) on the Examiner, it is respectfully submitted that it would be wasteful of the time, effort, and resources of both the applicant and the Patent Office to prosecute the claims to four compounds in four separate divisional applications. Search and examination of all groups of claims together would be much more efficient than requiring the Patent Office and the applicant to do so separately in five separate applications.

Noteworthy are the provisions of MPEP 1451 which provide the guidance that "Situations yielding divisional reissues occur *infrequently* and usually involve only two such files. It should be noted, however, that in *rare* instances in the past, there have been more than two (and as many as five) divisional reissues of a patent." (See p. 1400-1453, last paragraph, emphasis added). The small number and narrowness of the claims and the relatedness of the subject matter in this case certainly should not qualify as one of the rare and exceptional reissues requiring five applications as alleged by the Examiner.

In light of the above remarks, applicant respectfully requests that the Examiner reconsider and withdraw the restriction requirement.

ACTION REQUESTED

For the reasons set forth above, the petitioners hereby respectfully request the Patent Office withdraw the requirement for restriction and an early and favorable action on the merits on all pending claims in the application. In the alternative, the Applicant's request at a minimum, that Groups I and V be recombined into a single group, and Groups II-IV be recombined into a second group.

REQUEST FOR EXPEDITED HANDLING

In the final action, the application was rejected under 35 USC §251, the Examiner having alleged that the applicants have failed to allege an error that is correctable through reissue. Although the applicants have alleged that through error without deceptive intent, they failed to claim the full scope of their invention, and have presented broadening claims 9-12, the Examiner has challenged the sufficiency of the reissue application as explained above. In the most recent advisory action, the Examiner presently suggests that this application should be classified as a "no defect" reissue because claims 1-8 have no error and claims 9-12 have been restricted and withdrawn from consideration.

Together with this Petition requesting reconsideration of the final restriction requirement, the Applicants have filed a Notice of appeal. If this petition is successful, then one or more of claims 9-12 should be re-introduced into the application for examination on the merits. At that time, either the Patent Office will withdraw its rejection and examine the new claims on the merits, or will maintain its rejection under 35 USC §251, which is the subject of the appeal.

Because Applicant's period for appeal is running concurrently with this petition, and the decision on petition is crucial to issues on appeal, expedited handling of this petition is requested. Any fee required for expedited handling may be charged to deposit account number 13-2855.

Should the Patent Office wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the Patent Office is

urged to telephone the undersigned at the indicated number.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN

By: _____

Mark H. Hopkins, Ph.D.
Registration No. 44,775
Attorney for Applicants
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402
(312)-474-6300

April 5, 2002

Exhibit

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/313,534	05/13/99	ROMERO	A 4830.P-RE

HM12/0125

BRUCE STEIN
INTELLECTUAL PROPERTY LEGAL SERVICES
PHARAMACIA & UPJOHN COMPANY
KALAMAZOO MI 49001

EXAMINER	
MORRIS P	
ART UNIT	**PAPER NUMBER**
1625	12

DATE MAILED: 01/25/01

RESPONSE DUE April 25, 2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/313,534	Romero
Examiner	**Group Art Unit**
T. Wells	1631

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1 - 12 is/are pending in the application.

Of the above claim(s) 9 - 12 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1 - 8 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

DETAILED ACTION

Reissue Applications

Claims 1-8 are consideration in this application.

Claims 9-12 are held withdrawn from consideration as being drawn to nonelected subject matter 37 CFR 1.142(b).

Continued Prosecution Application

The request filed on Dece,ber 11, 2000for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/313,534 is acceptable and a CPA has been established. An action on the CPA follows.

Applicant's communication filed December 11, 2000 is noted. **To clarify the record, there was never any formal interview of December 4, 2000 with the alleged attorney of record. The examiner NEVER AGREED that the filing of the present CPA, after two years from the grant of the original patent would have no impact on the applicants' right to file to enlarge the scope of the claims, that are subject of the instant reissue. This is a false and inaccurate allegation by applicants.**

A CPA is a technically/legally a new application. Hence, applicant has now added an additional issue of broadening the claims outside the two year period. Further, new rule 37 CFR 1.176 is applicable herein.

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-12, drawn to compounds, composition and use, classified in class 514, subclass 292.

II. Claim 9, drawn to an intermediate, classified in class 546, subclass 158.

III. Claim 10, drawn to an intermediate, classified in class 546, subclass 159.

IV. Claim 11, drawn to an intermediate, classified in class 546, subclass 162.

V. Claim 12, drawn to an intermediate, classified in class 546, subclass 84.

These distinct inventions have acquired separate status in the art, will support separate patents, and will require different fields of search for the respective inventions. Accordingly, restriction for examination purposes as indicated is considered proper; 35 U.S.C. 121; 37 CFR 1.141; 37 CFR 1.142.

Inventions I and II-V are related as mutually exclusive species in an intermediate-final product relationship. Distinctness is proven for claims in this relationship if the intermediate product is useful to make other than the final product (MPEP § 806.04(b), 3rd paragraph), and the species are patentably distinct (MPEP § 806.04(h)). In the instant case, the intermediate product is deemed to be useful as herbicides, fungicides, bactericides, insecticides, etc., and the inventions are deemed patentably distinct since there is nothing on this record to show them to be obvious variants. Should applicant traverse on the ground that the species are not patentably

distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions anticipated by the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

The subject matter of the original patent claims are held to be constructively elected. Hence, claims 9-12 are held withdrawn from consideration as being drawn to nonelected subject matter.

The reissue oath or declaration filed December 11, 2000 application is defective because none of the errors which are relied upon to support the reissue application are errors upon which a reissue can be based. See 37 CFR 1.175(a)(1) and see MPEP 1414.

The reissue statute - 35 U.S.C. 251 - provides for the reissue of patents whenever the patent is deemed wholly or partly inoperative or invalid through error without any deceptive intention. Applicant fails to allege that the original patent is inoperative or invalid or fails to state the reason of a defective specification, or of patentee claiming more or less that patentee had the right to claim in the patent.

Applicant now merely asserts in the declaration filed December 11, 2000 that applicant failed to claim intermediates. Applicant has added claims directed to inventions which are

separate and distinct from the invention defined by the original patent claims. This has been clearly set forth in the record. The Office does not allow a reissue patent which does not correct any error in the original patent. Note 37 CFR 1.145 and new rule 1.176 effective November 7, 2000.

Again, the reissue oath/declaration filed with this application is defective because it fails to identify at least one error which is relied upon to support the reissue application. See 37 CFR 1.175(a)(1) and MPEP § 1414. There is no error in the original patent claims.

The reissue oath/declaration filed with this application is defective because it fails to contain a statement that all errors which are being corrected in the reissue application up to the time of filing of the oath/declaration arose without any deceptive intention on the part of the applicant. See 37 CFR 1.175 and MPEP § 1414.

Claims 1-8 are rejected as being based upon a defective reissue declaration under 35 U.S.C. 251 as set forth above. See 37 CFR 1.175.

As clearly set forth above, there is no error in the original patent claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ms. Morris whose telephone number is (703) 308-4533.

plm

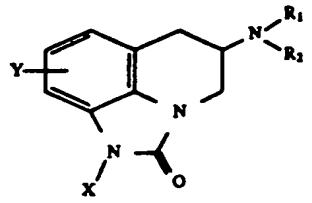
January 24, 2001

PATRICIA L. MORRIS
PRIMARY EXAMINER
GROUP 120

Exhibit

What is claimed is:

1. A compound of the following structural formula:



and pharmaceutically acceptable salts thereof wherein.

R_1 and R_2 are independently hydrogen, C_{1-6} alkyl or R_1 and R_2 are joined to form pyrrolidine, piperidine, morpholine or imidazole;

X is OCH_3, SO_2R_3, SO_2CF_3 or CN;

R_3 is C_{1-6} alkyl or a C_{5-10} aromatic ring (optionally substituted with a halogen, hydroxyl or C_{1-6} alkyl (optionally substituted with halogen or hydroxyl); and

Y is hydrogen, Cl, Br, F, CN, $CONR_1R_2$, CF_3, OCH_3, $SO_2NR_1R_2$.

2. The compound of claim 1 wherein R_1 and R_2 are each propyl.

3. The compound of claim 1 wherein R_1 and R_2 are each methyl.

4. The compound of claim 1 wherein X is —OCH_3.

5. The compound of claim 1 wherein Y is hydrogen.

6. The compound of claim 1 which is

a) (R)-5-Methylamino-1-methoxy-5,6-dihydro-4H-imidazo[4,5,1-ij]-quinolin-2(1H)-one,

b) (R)-5-Dimethylamino-1-methoxy-5,6-dihydro-4H-imidazo[4,5,1-ij]-quinolin-2(1H)-one,

c) (R)-5-Propylamino-1-methoxy-5,6-dihydro-4H-imidazo[4,5,1-ij]-quinolin-2(1H)-one, or

d) (R)-5-Dipropylamino-1-methoxy-5,6-dihydro-4H-imidazo[4,5,1-ij]-quinolin-2(1H)-one.

7. A method for treating anxiolylic disorders in animal or human hosts comprising the administration of a pharmaceutically effective amount of a compound of Formula I as set forth in claim 1.

8. The method of claim 7 wherein said compound is orally administered in an amount of from about 10 mg to about 1200 mg per day.

* * * * *

9. (R)-3-Methylamino-1,2,3,4-tetrahydroquinoline maleate.

10. (R)-Methyl-(1,2,3,4-tetrahydro-3-quinolinyl) carbamic acid, phenylmethyl ester.

11. (R)-Methyl-[1,2,3,4-tetrahydro-1-[(methoxyamino)carbonyl]-3-quinolinyl]carbamic acid, phenylmethyl ester.

12. Methyl-(1,2,5,6-tetrahydro-1-methoxy-2-oxo-4H-imidazo[4,5,1-ij]quinolinyl-5-yl)carbamic acid, phenylmethyl ester.

Exhibit

* * * * * * * * * * Welcome to STN Inte rnational * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar S chedule - N. America
NEWS 2	Jan 25	BLAST(R) searching in REGISTRY available in STN on the Web
NEWS 3	Jan 25	Searching with the P indicator for Preparations
NEWS 4	Jan 29	FSTA has been reloaded and move s to weekly updates
NEWS 5	Feb 01	DKILIT now produced by FIZ Karl sruhe and has a new update frequency
NEWS 6	Feb 19	Access via Tymnet and SprintNet Eliminated Effective 3/31/02
NEWS 7	Mar 08	Gene Names now available in BIO SIS
NEWS 8	Mar 22	TOXLIT no longer available
NEWS 9	Mar 22	TRCTHERMO no longer available
NEWS 10	Mar 28	US Provisional Priorities searc hed with P in CA/CAplus and USPATFULL
NEWS 11	Mar 28	LIPINSKI/CALC added for propert y searching in REGISTRY
NEWS 12	Apr 02	PAPERCHEM no longer available o n STN. Use PAPERCHEM2 instead.

NEWS EXPRESS	February 1 CURRENT WINDOWS VERSION IS V 6.0d, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
NEWS HOURS	STN Operating Hours Plus Help Desk Av ailability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Net work Access to STN
NEWS WWW	CAS World Wide Web Site (general in formation)

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* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 18:29:53 ON 05 APR 2002
ENTER COST CENTER (NONE): 28341/10101
CHARGED TO COST=28341/10101

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 18:30:13 ON 05 APR 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN C USTOMER AGREEMENT.
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STRUCTURE FILE UPDATES: 3 APR 2002 HI GHEST RN 403978-70-1
DICTIONARY FILE UPDATES: 3 APR 2002 HI GHEST RN 403978-70-1

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

The P indicator for Preparations was not generated for all of the CAS Registry Numbers that were added to the H/Z/CA/CAplus files between 12/27/01 and 1/23/02. Use of the P indicator in online and SDI searches during this period, either directly appended to a CAS Registry Number or by qualifying an L-number with /P, may have yielded incomplete results. As of 1/23/02, the situation has been resolved. Also, note that searches conducted using the PREP role indicator were not affected.

Customers running searches and/or SDIs in the H/Z/CA/CAplus files incorporating CAS Registry Numbers with the P indicator between 12/27/01 and 1/23/02, are encouraged to re-run these strategies. Contact the CAS Help Desk at 1-800-848-6533 in North America or 1-614-447-3698, worldwide, or send an e-mail to help@cas.org for further assistance or to receive a credit for any duplicate searches.

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=>
L1       STRUCTURE UPLOADED

=> s l1 full exact
FULL SEARCH INITIATED 18:32:29 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -       2 TO ITERATE

100.0% PROCESSED        2 ITERATIONS                                    1 ANSWERS
SEARCH TIME: 00.00.01

L2             1 SEA EXA FUL L1

=> dis l2

L2    ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN    222415-94-3  REGISTRY
CN    Carbamic acid, methyl[(5R)-1,2,5,6-tetrahydro-1-methoxy-2-oxo-4H-
      imidazo[4,5,1-ij]quinolin-5-yl]-, phenylmethyl ester (9CI)  (CA INDEX
      NAME)
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MF    C20 H21 N3 O4
SR    CA
LC    STN Files:   CA, CAPLUS, USPATFULL

Absolute stereochemistry.  Rotation (+).
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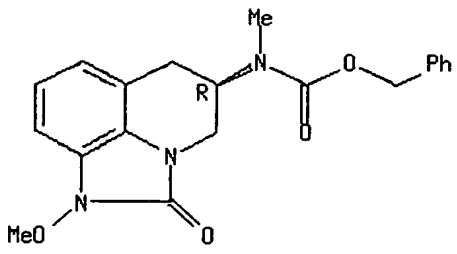

PROPERTY DATA AVAILABLE IN THE 'PROP' F ORMAT

1 REFERENCES IN FILE CA (1 967 TO DATE)
1 REFERENCES IN FILE CAPLU S (1967 TO DATE)

=>
L3 STRUCTURE UPLOADED

=> s l3 full exact
FULL SEARCH INITIATED 18:34:09 FILE 'REGI STRY'
FULL SCREEN SEARCH COMPLETED - 2 TO ITERATE

100.0% PROCESSED 2 ITERATIONS 1 ANSWERS
SEARCH TIME: 00.00.01

L4 1 SEA EXA FUL L3

=>
L5 STRUCTURE UPLOADED

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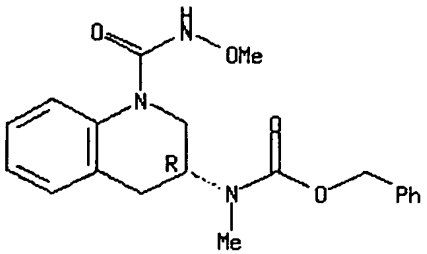

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2 REFERENCES IN FILE CAPLU S (1967 TO DATE)

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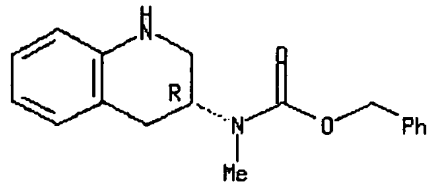

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100.0% PROCESSED 87 ITERATIONS 1 ANSWERS
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L8 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2 002 ACS
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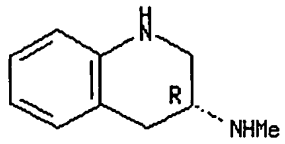
Absolute stereochemistry. Rotation (+).



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FULL ESTIMATED COST	198.88	199.09

FILE 'HCAPLUS' ENTERED AT 18:37:40 ON 05 APR 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN C USTOMER AGREEMENT.
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FILE COVERS 1907 - 5 Apr 2002 VOL 136 ISS 14
FILE LAST UPDATED: 3 Apr 2002 (20020403/ ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective De cember 16, 2001. Please check your SDI profiles to see if they ne ed to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in th is file.

The P indicator for Preparations was not generated for all of the CAS Registry Numbers that were added to t he CAS files between 12/27/01 and 1/23/02. As of 1/23/02, the situatio n has been resolved. Searches and/or SDIs in the H/Z/CA/CAplus files in corporating CAS Registry Numbers with the P indicator executed bet ween 12/27/01 and 1/23/02 may be incomplete. See the NEWS message on t his topic for more information.

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L9 1 L2

=> dis 19

L9 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 20 02 ACS

Full Text | Citing References

AN 1999:233800 HCAPLUS
DN 130:272022
TI Sustained-release tablet formulation to treat Parki nson disease
IN Ju, Tzu-chi Robert
PA Pharmacia & Upjohn Company, USA
SO PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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	US 6197339	B1	20010306	US 1998-146090	19980930
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	NO 2000001624	A	20000329	NO 2000-1624	20000329
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	US 1998-146090	A1	19980930		

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L10 2 L4

=> dis l10 1-2

L10 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 20 02 ACS

Full Text | Citing References

AN 1999:233800 HCAPLUS
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	WO 9916442	A3	19990617		

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	US 2001053386	A1	20011220	US 2001-759286	20010111
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L10 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 20 02 ACS

Full Text | Citing References

AN 1995:750538 HCAPLUS
DN 123:143891
TI Heterocyclic amines having central n ervous system activity
IN Romero, Arthur G.
PA Upjohn Co., USA
SO PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

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OS MARPAT 123:143891

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L11 2 L6

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L11 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 20 02 ACS
Full Text | Citing References

AN 1999:233800 HCAPLUS
DN 130:272022
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PA Pharmacia & Upjohn Company, USA
SO PCT Int. Appl., 17 pp.
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FAN.CNT 1

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L11 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 20 02 ACS
Full Text | Citing References

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FAN.CNT 2

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L12 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 20 02 ACS

Full Text | Citing References

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	JP 09500898	T2	19970128	JP 1994-505808	19940617
	AT 159943	E	19971115	AT 1994-921952	19940617
	ES 2108474	T3	19971216	ES 1994-921952	19940617
	CN 1128030	A	19960731	CN 1994-192910	19940627
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	US 5652245	A	19970729	US 1996-592328	19960123
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OS MARPAT 123:143891

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LOGOFF? (Y)/N/HOLD: y

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HCAPLUS FILE	28 341/10101	0.06	18.57
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Exhibit

US005932553A

United States Patent [19]

McMorris et al.

[11] Patent Number: 5,932,553

[45] Date of Patent: Aug. 3, 1999

[54] **ILLUDIN ANALOGS USEFUL AS ANTITUMOR AGENTS**

[75] Inventors: Trevor C. McMorris; Michael J. Kelner, both of LaJolla, Calif.

[73] Assignee: The Regents of the University of California

[21] Appl. No.: 08/683,687

[22] Filed: Jul. 18, 1996

[51] Int. Cl.[6] A61K 31/12; A61K 31/70; A61K 31/215; C07C 49/737

[52] U.S. Cl. 514/23; 514/546; 514/678; 514/681; 514/691; 562/553; 568/374

[58] Field of Search 514/23, 546, 678, 514/681, 691; 562/553; 568/374

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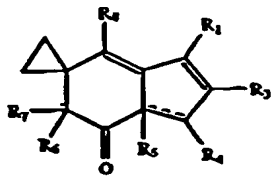
(List continued on next page.)

Primary Examiner—John Kight
Assistant Examiner—Howard C. Lee
Attorney, Agent, or Firm—Schwegman, Lundberg, Woessner & Kluth, P.A.

[57] **ABSTRACT**

The present invention provides illudin analogs of the general formula (I):

(I)



where R_1 is $(CH_2)_n$—X—Y or H; n is 0 to 4; X is O or S or N or absent; and Y is an optionally substituted $(C_1–C_6)$alkyl, $(C_6–C_{10})$aryl, $(C_6–C_{10})$aryl$(C_1–C_4)$alkyl or cyclo$(C_3–C_6)$ alkyl optionally comprising one or more heteroatoms; a monosaccharide, an amino acid residue, or H when n is 2–4; R_2 is absent; or R_1 and R_2 together comprise a 5–7 membered cyclic ring;

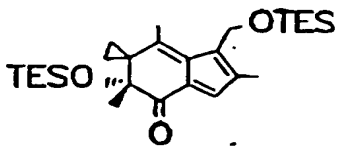
R_3 is $(C_1–C_4)$alkyl or H; R_4 is H, SCH_2CO_2 $(C_1–C_4)$alkyl, O—$(C_5–C_{12})$aryl or —S—$(C_5–C_{12})$aryl; R_5 is H, OH or absent; R_6 is $(C_1–C_4)$alkyl or absent; R_7 is OH or OSi$((C_1–C_4)alkyl)_3$; or

R_6 and R_7 together are ethylenedioxy;

R_8 is optionally substituted $(C_1–C_4)$alkyl; and

the bonds represented by — are individually present or absent. The invention further provides dimers comprising analogs of formula (I).

57 Claims, 7 Drawing Sheets



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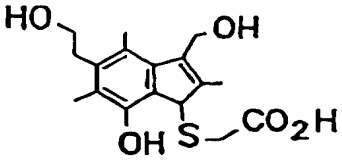

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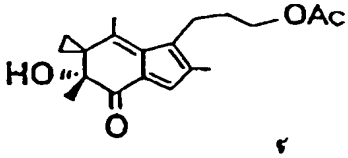

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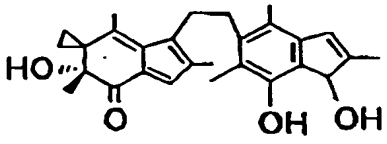

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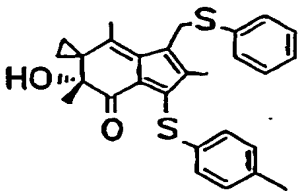

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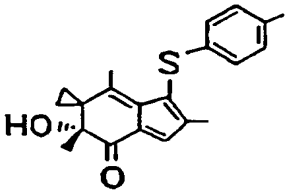

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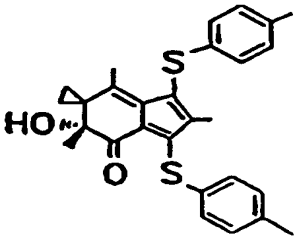

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FIG. 1D

3.58 (m, 4H), 3.86 (m, 1H), 3.91 (s, 1H), 4.51 (q, J_{AB}=12.9 Hz, 2H), 7.10 (s, 1H); ^{13}C NMR ($CDCl_3$) δ198.0, 160.1, 143.2, 138.8, 134.6, 129.4, 126.9, 76.2, 70.9, 70.6, 64.4, 63.8, 37.6, 27.4, 16.1, 14.2, 13.1, 9.4; MS m/z 320 (M^+), 277, 228, 185; HRMS for $C_{16}H_{24}O_5$ calcd 320.1623, found 320.1616; UV λmax (methanol) 331 nm (ε7920).

Compound 20 & 53

To the solution of 188 mg HMAF (MW 246, 0.764 mmol) in 10 ml acetone and 1 M H_2SO_4 solution (1:1) was added 5 ml 2-bromoethanol. The mixture was stirred at room temperature for 4.5 h and was partitioned between ethyl acetate and water. The organic extracts were washed by saturated $NaHCO_3$ and saline respectively to neutral. After being dried by $MgSO_4$, the solution was concentrated and chromatographed to give 179.2 mg 20 (66.4%) as yellow gum: IR (KBr) 3445, 2914, 1650, 1592, 1502, 1097 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ0.71 (m, 1H), 1.07 (m, 1H), 1.35 (m, 1H), 1.38 (s, 3H), 1.48 (m, 1H), 2.15 (s, 3H), 3.47 (t, J=6.0 Hz, 2H), 3.77 (t, J=6.0 Hz, 2H), 3.91 (s, 1H), 4.54 (q, J_{AB}=12 Hz, 2H), 7.09 (s, 1H); ^{13}C NMR ($CDCl_3$) δ198.1, 160.6, 143.2, 138.9, 134.4, 129.3, 127.0, 76.3, 69.4, 64.1, 37.7, 30.6, 27.6, 16.4, 14.3, 13.2, 9.5; MS m/z 352 (M–H), 326, 228, 285; HRMS for $C_{17}H_{21}BrO_5$ (M–H) calcd 352.0574, found 352.0671; UV λmax (methanol) 332 nm (ε 7777). 53 was obtained as by product as a yellow gum: ^{1}H NMR ($CDCl_3$) δ0.72 (m, 1H), 1.05 (m, 1H), 1.32 (m, 1H), 1.37 (s, 3H), 1.50 (m, 1H), 2.13 (s, 3H), 2.15 (s, 3H), 3.46 (t, J=6.3 Hz, 2H), 3.65 (m, 4H), 3.79 (t, J=6.3 Hz, 2H), 3.90 (s, 1H), 4.51 (q, J_{AB}=12 Hz, 2H), 7.09 (s, 1H).

Compound 21

To the solution of 260 mg HMAF (MW 246, 1.057 mmol) in 6 ml 2-methoxyl propene was added 2 drops $POCl_3$. The mixture was stirred at room temperature for 6 days and was partitioned between ethyl acetate and water. The organic extracts were washed by saturated $NaHCO_3$ and saline respectively to neutral. After being dried by $MgSO_4$, the solution was concentrated and chromatographed to give 133 mg 21 (39.6%) as yellow gum (with 87 mg HMAF recycled): IR (KBr) 3457, 2980, 1665, 1598, 1502, 1091 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ0.72 (m, 1H), 1.06 (m, 1H), 1.25 (m, 1H), 1.38 (s, 3H), 1.41, (s, 3H), 1.42 (s, 3H), 1.49 (m, 1H), 2.15 (s, 3H), 3.25 (s, 6H), 3.95 (s, 1H), 4.43 (s, 2H), 7.11 (s, 1H); ^{13}C NMR ($CDCl_3$) δ197.7, 159.5, 142.2, 134.9, 134.8, 130.5, 126.7, 100.3, 76.1, 54.4, 48.6, 37.4, 27.5, 24.4, 24.3, 15.9, 14.0, 13.0, 9.3; MS m/z 318 (M^+), 260, 229, 185, 73; HRMS for $C_{19}H_{26}O_4$ calcd 318.1831, found 318.1823; UV λmax (methanol) 330 nm (ε 8728).

Compound 22

To the solution of 9.0 mg HMAF (MW 246, 0.037 mmol) in 9 ml acetone and 1 M H_2SO_4 solution (1:1) was added 4.5 ml ethylene glycol. The mixture was stirred at room temperature for 2 h and was partitioned between ethyl acetate and water. The organic extracts were washed by saturated $NaHCO_3$ and saline respectively to neutral. After being dried by $MgSO_4$, the solution was concentrated and chromatographed to give 11 mg 22 (100%) as yellow gum: IR(KBr) 3439, 2914, 1665, 1598, 1508, 1344, 1103 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ0.71 (m, 1H), 1.06 (m, 1H), 1.32 (m, 1H), 1.36 (s, 3H), 1.47 (m, 1H), 2.11 (s, 3H), 2.14 (s, 3H), 2.55 (s, 1H), 3.57 (t, J=4.5 Hz, 2H), 3.73 (t, J=4.5 Hz, 2H), 3.98 (s, 1H), 4.50 (q, J_{AB}=12 Hz, 2H), 7.09 (s, 1H); ^{13}C NMR ($CDCl_3$) δ197.9, 160.0, 142.9, 138.9, 134.5, 129.6, 126.8, 76.1, 70.9, 64.2, 61.6, 37.5, 27.4, 16.0, 14.1, 13.1, 9.3; MS m/z 290 (M^+), 250, 228, 185; HRMS for $C_{17}H_{22}O_4$ calcd 290.1518, found 190.1515; UV λmax (methanol) 331 nm (ε 9404).

Compound 10 & 13

To the solution of 1 g fulvene (MW 216, 4.63 mmol) in 5 ml acetone and 2.5 ml 2 M H_2SO_4 solution was added 2.5 ml acrolein. The mixture was stirred at room temperature for 7 h and was partitioned between ethyl acetate and water. The organic extracts were washed by samrated $NaHCO_3$ and saline respectively to neutral. After being dried by $MgSo_4$, the solution was concentrated and chromatographed to give 378 mg 10 (30.0%) and 241 mg 13 (13.6%). 10 is a yellow gum: 0.68 (m, 1H), 1.07 (m, 1H), 1.32 (m, 1H), 1.36 (s, 3H), 1.46 (m, 1H), 2.01 (s, 3H), 2.06 (s, 3H), 2.65 (t, J=7.8 Hz, 2H), 3.00 (m, 2H), 3.93 (s, 1H), 7.12 (s, 1H), 9.83 (s, 1H); ^{13}C NMR ($CDCl_3$) δ200.4, 196.3, 157.3, 139.4, 138.3, 135.4, 133.7, 125.3, 75.4, 43.5, 36.9, 27.0, 19.5, 15.4, 13.4, 12.4, 8.6; MS m/z 272 (M^+), 244, 215, 201; HRMS for $C_{17}H_{20}O_3$ calcd 272.1413, found 272.1416; UV λmax (methanol) 332 nm (ε 8500). 13 is also a yellow gum (mixture): HRMS for $C_{23}H_{28}O_5$ calcd 384.1937, found 384.1947; UV λmax (methanol) 329 nm (ε 6000).

Compound 30, 31 & 45

To the solution of 108 mg HMAF (MW 246, 0.439 mmol) in 40 ml acetone and THF (1:1) was added 1.5 ml methyl thioglycolate. The mixture was stirred at room temperature for 4 days and was partitioned between ethyl acetate and water. The organic extracts were dried by $MgSO_4$, concentrated and chromatographed to give 44 mg 30, 20 mg 31 and 29 mg 45. 30 is a yellow gum: ^{1}H NMR ($CDCl_3$) δ0.70 (m, 1H), 1.09 (m, 1H), 1.33 (s, 3H), 1.35 (m, 1H), 1.50 (m, 1H), 2.14 (s, 3H), 2.15 (s, 3H), 3.23 (s, 2H), 3.67 (s, 3H), 3.74 (s, 3H), 3.92 (s, 2H), 4.08 (m, 3H); MS m/z 438 (M^+), 424, 333, 315; HRMS for $C_{21}H_{26}O_6S_2$ calcd 438.1172, found 438.1188; UV λmax (methanol) 372 nm (ε 10760), 243 nm (ε14364). 31 is a light yellow gum: ^{1}H NMR ($CDCl_3$) δ0.46 (m, 1H), 0.88 (m, 1H), 1.04 (m, 1H), 1.32 (s, 3H), 1.38 (m, 1H), 1.87 (s, 3H), 2.03 (s, 3H), 3.13 (m, 2H), 3.44 (m, 3H), 3.73 (s, 3H), 3.77 (s, 3H), 4.02 (s, 1H), 4.41 (q, 2H); MS m/z 456 (M^+), 425, 351, 333; HRMS for $C_{21}H_{28}O_7S_2$ calcd 456.1277, found 456.1288; UV λmax (methanol) 263 nm (ε 17264), 204 nm (ε 8648). 45 is also a yellow gum: MS m/z 352 (M^+), 334, 263, 244, 229, 201; HRMS for $C_{18}H_{24}O_5S$ calcd 352.1345, found 352.1333; UV λmax (methanol) 328 nm (ε 2692), 238 nm (ε 11099).

Compound 9

To the solution of 30 mg 10 (MW 272, 0.110 mmol) in 5 ml THF was added 5 drops HOAc and some sodium cyanoborohydride. The mixture was stirred at room temperature for 1 h and was partitioned between ethyl acetate and water. The organic extracts were washed by saturated NH_4Cl and saline respectively to neutral. After being dried by $MgSO_4$, the solution was concentrated and chromatographed to give 21 mg 9 (69.5%) as yellow gum: ^{1}H NMR ($CDCl_3$) δ0.67 (m, 1H), 1.06 (m, 1H), 1.26 (m, 1H), 1.36 (s, 3H), 1.46 (m, 1H), 1.73 (m, 2H), 2.06 (s, 3H), 2.07 (s, 3H), 2.74 (m, 2H), 3.70 (t, J=6.3 Hz, 2H), 3.96 (s, 1H), 7.14 (s, 1H); ^{13}C NMR ($CDCl_3$) δ197.0, 157.7, 139.6, 139.0, 136.6, 136.5, 128.2, 75.9, 62.0, 37.3, 33.0, 27.5, 24.0, 15.9, 13.8, 12.8, 9.0; MS m/z 274 (M^+), 246, 215, 187; HRMS for $C_{17}H_{22}O_3$ calcd 274.1569, found 274.1557; UV λmax (methanol) 330 nm (ε 6700).

Compound 27

To the solution of 163 mg HMAF (MW 246, 0.663 mmol) in 10 ml methylene chloride was added 0.18 ml pyridine and 0.34 ml phenyl chloroformate at 0° C. under argon. The mixture was stirred for 3 h and was partitioned between ethyl acetate and water. The organic extracts were washed with saline. After being dried by $MgSO_4$, the solution was